STRUCTURE OF DEMETHYLTUBULOSINE: A TOTAL SYNTHESIS OF (±)-10-DEMETHYLTUBULOSINE

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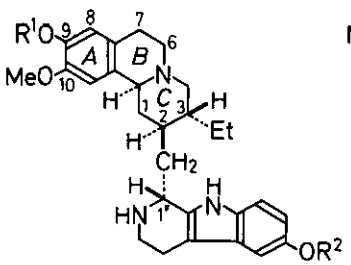
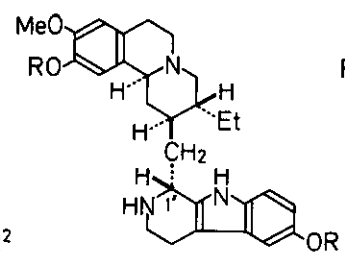
Abstract —— (±)-10-Demethyltubulosine (IV) has been synthesized from the tricyclic amino acid VI through the intermediates VII, VIII, and V. Identity of synthetic (±)-IV with natural (−)-demethyltubulosine unequivocally established the structure of this Alangium alkaloid.

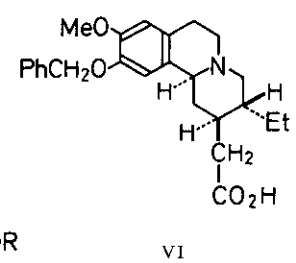
Demethyltubulosine is a phenolic alkaloid isolated from Alangium lamarckii Thw. (Alangiaceae).[1,2] Popelak and co-workers[1] proposed the structure I or IV for this compound on the basis of its two-step methylation to O-methyltubulosine (III) through tubulosine (II) and on the mass spectral evidence. Quite recently, Fujii and co-workers[3] synthesized (±)-9-demethyltubulosine (I) and found that it was not identical with natural demethyltubulosine. This indicated the alternative 10-demethyl structure (IV) to be the correct expression for this Alangium alkaloid. Now we wish to report the results of our further efforts directed toward the synthesis of (±)-IV, which have confirmed the structure of demethyltubulosine.



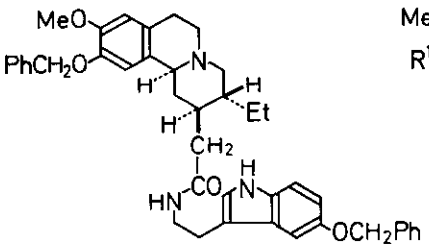
I: R^1 = H; R^2 = H
II: R^1 = Me; R^2 = H
III: R^1 = Me; R^2 = Me



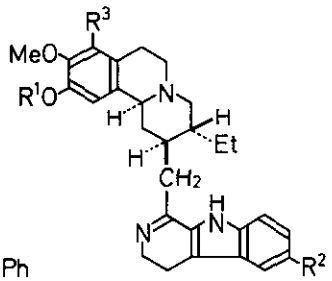
IV: R = H
V: R = $PhCH_2$



VI



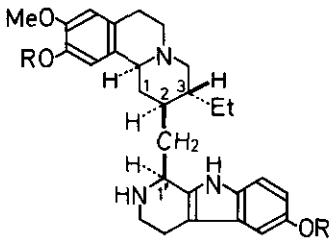
VII



VIII: R^1 = $PhCH_2$; R^2 = $PhCH_2O$; R^3 = H

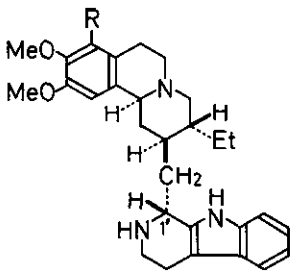
IX: R^1 = Me; R^2 = H; R^3 = H

X: R^1 = Me; R^2 = H; R^3 = $PhCH_2O$



XI: R = $PhCH_2$

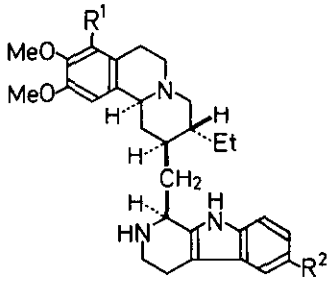
XII: R = H



XIII: R = H

XIV: R = $PhCH_2O$

XV: R = OH

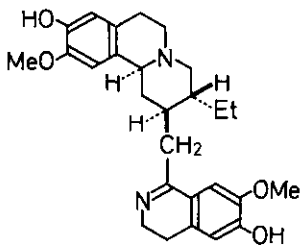


XVI: R^1 = H; R^2 = H

XVII: R^1 = H; R^2 = OH

XVIII: R^1 = $PhCH_2O$; R^2 = H

XIX: R^1 = OH; R^2 = H



XX

The key intermediate selected for the synthesis of the target molecule [(±)-IV] was the racemic tricyclic amino acid VI, and it was prepared in eight steps from ethyl (±)-trans-5-ethyl-2-oxo-4-piperidineacetate[4] according to the recently reported procedure[5] ("lactim ether method"[6]). Condensation of VI with 5-benzyloxytryptamine[7] using the coupling reagent diethyl phosphorocyanidate[8] (Et_3N, $HCONMe_2$, room temp., 6 h) produced the amide VII (mp 150.5–152°C)[9] in 96% yield. The amide VII was then subjected to dehydrocyclization with $POCl_3$ in boiling toluene for 2.5 h to give the dihydro-β-carboline VIII (59% yield) as a yellow glass, which was hydrogenated with hydrogen and Adams catalyst (dioxane, 1 atm, 19°C, 1.5 h). Chromatographic separation (silica gel, $CHCl_3$–EtOH) of the hydrogenation products furnished (±)-O,O-dibenzyl-10-demethyltubulosine (V) [25% yield; ^{1}H nmr ($CDCl_3$) δ:[10] 3.83 (3H, s, OMe), 5.08 (4H, s, C(10)-O$\underline{CH_2}$Ph and C(6′)-O$\underline{CH_2}$Ph); ^{13}C nmr ($CDCl_3$) δ:[10] 36.3 (C-2), 36.8 (C-1), 49.3 (C-1′)][11] and its 1′-epimer (XI) [54% yield; ^{1}H nmr ($CDCl_3$) δ: 3.80 (3H, s, OMe), 4.92 (2H, s, C(10)-O$\underline{CH_2}$Ph), 5.01 (2H, s, C(6′)-O$\underline{CH_2}$Ph); ^{13}C nmr ($CDCl_3$) δ: 38.4 (C-2), 38.9 or 39.2 (C-1), 52.3 (C-1′)] as glassy substances.

In line with our studies[3] on (±)-I and its 1-epimer as well as their O,O-dibenzyl derivatives, the assignments of the relative configuration at C-1′ of V and XI were based on the following evidence. The formation of V and XI in a 1 : 2.2 molar ratio on hydrogenation of VIII was comparable to that of deoxytubulosine (XIII) and isodeoxytubulosine (XVI) in a 1 : 2 molar ratio[12] or to that of O-benzylalangimarckine (XIV) and its 1′-epimer (XVIII) in a 1 : 1.9 molar ratio[13] in a similar hydrogenation of the dihydro-β-carboline IX or X. On thin-layer chromatography [silica gel, $CHCl_3$–EtOH (10 : 1, v/v)], V moved faster than its 1′-epimer XI, and this behavior corresponded to that[14] found for a pair of tubulosine (II)[12,14–16] and isotubulosine (XVII)[12,14,16] and to that[13,17] observed for a pair of XIV and XVIII or of alangimarckine (XV) and its 1′-epimer (XIX). In the ^1H nmr spectra of V and XI in $CDCl_3$ (vide supra), the methylene protons of the C(10)-benzyloxy group in XI were more shielded than those in V by 0.16 ppm. Such an upfield shift observed for the 1′-epimer has also been found[14,17] for the C(10)-methoxyl protons of isotubulosine (XVII) or XIX and not for those of tubulosine (II) or alangimarckine (XV). The ^{13}C nmr data also fulfilled a reliable criterion upon which to test the stereochemical relationship. The C-1, C-2, and C-1′ carbon signals of V resonated at higher field than the corresponding ones of XI by 2.1–3.0 ppm. This feature was similar to that found by Wenkert et al.[18] for ochrolifuanine A and ochrolifuanine B, a 1′-epimeric pair of indoloquinolizidine-type analogues, and to that[17] observed by us for a pair of alangimarckine (XV) and its 1′-epimer (XIX).

On catalytic hydrogenolysis [Pd-C/H_2, MeOH–AcOH (1 : 1, v/v), 1 atm, 18°C, 3 h], V afforded the desired phenolic base (±)-IV (79% yield), which was characterized as a dihydrate [mp 199–201°C (dec.); ^1H nmr (Me_2SO-d_6) δ:[10] 3.72 (3H, s, OMe)]. A similar debenzylation of the epimeric base XI gave the corresponding phenolic base (±)-XII [mp 215–217°C (dec.);[19] ^1H nmr (Me_2SO-d_6) δ: 3.71 (3H, s, OMe)] in 88% yield. It was found that the uv (MeOH, 0.1 N aq. HCl, or 0.1 N aq. NaOH), ir (Nujol), ^1H nmr (Me_2SO-d_6), and mass spectra and chromatographic behavior of the synthetic (±)-IV were identical with those of natural (–)-demethyltubulosine dihydrate[1] [mp 198–200°C (dec.)].

Thus, the above results establish the structure of the Alangium alkaloid demethyltubulosine as 10-demethyltubulosine [IV (absolute configuration shown)]. It is of interest to note that the positions of the methoxyl and the hydroxyl groups in ring *A* of this base are just the reverse of those of desmethylpsychotrine (XX),[2,5,20] a co-occurring alkaloid.[2]

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10. In ppm downfield from internal tetramethylsilane.
11. Crystallized from EtOH in colorless needles, mp 89–91°C, which were found to contain 0.5 equivalent mole of EtOH of crystallization.
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19. The analysis pointed to the formula $C_{28}H_{35}N_3O_3 \cdot 2/3\,H_2O$.
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